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REVIEWER

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 28 1987

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Chlordimeform 6(a)(2) data notifications.
Caswell File #174A.

FROM: Stanley B. Gross, Ph.D., Toxicologist
Section 7, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Stanley B Gross 4/23/87

TO: Walter Waldrop/Doug McKinnev PM-63
Special Review Branch
Registration Division (TS-767C)

THRU: Albin B. Kocialski, Ph.D., Supervisory Pharmacologist
Section 7, Toxicology Branch
Hazard Evaluation Division (TS-769C)

ABK 4/28/87

and

Theodore M. Farber, Ph.D., Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

4/28/87

Request:

Ciba-Geigy Corporation has submitted the following reports as 6(a)(2) data:

1) A 1985 epidemeological cancer study from a Hoescht AG dye plant in Germany and follow-up letters from Hoechst AG, Germany, American Hoechst Corporation and an Australian medical officer.

2) A mouse feeding oncogenicity study carried out in China using chlordimeform and 4-chloro-o-toluidine.

3) A mouse skin painting oncogenicity study carried out in China using chlordimeform desolved in croton oil and acetone.

4) Worker exposure study from a Chinese chlordimeform packing plant.

5) A urinary excretion study in Chinese farmers spraying chlordimeform.

80

The four reports of Chinese investigations were published in the Occupational Health Bulletin in 1985 and subsequently tranlated.

Registration Division has asked that these submissions be examined to see if they have a significant impact on the special review of chlordimeform currently in process.

Summary Recommendatons.

Specific recommendations regarding each study are presented below. None of the above reports provide information to change the hazard assessment for chlordimeform which has already been developed.

Background Information.

Chlordimeform (as the base or the hydrochloride salt) has been used as an insecticide/acaricide with ovicidal properties. The agent was introduced in 1966 by Schering A.G., Germany and Ciba-Geigy, Switzerland. Chlordimeform (CDM) had been used widely on a large number of crops until it was voluntarily removed from the market in 1976 when it was found to cause cancer in mice. The primary cancer lesion was hemangiosarcoma, a vascular tumor which was found distributed in several organs of the affected mice. These lesions were not found in long-term studies in the rat or dog. Chlordimeform was allowed back on the market in the early 1980's after Ciba-Geigy and Nor Am developed a program to protect workers using protective clothing and closed mixing systems.

Chlordimeform was the subject of a Registration Standard in 1984. The Toxicology Chapter and Standard was completed in 1985 and the Guidance Package, early in 1986. A Special Review of chlordimeform was begun in 1986 because, among other questions, there was concern for the amount of exposure applicators were receiving. Measurable amounts of chlordimeform metabolites were found in worker urine. One of the metabolites found in human and animal urine, 4-chloro-o-toluidine, is assumed to be carcinogeni One question which remains is whether worker exposures can be adequately controlled so as to adequately protect the workers.

REVIEW OF SUBMITTED STUDIES

A. German Dye Plant Epidemeology Study

Study: A historic Cohort Study of 4-chloro-2 methyl-aniline Workers. Stasik, M.J., Lange, H. -J.; Ulm, K. and Schuckmann, F. Department of Occupational Medicine, Hoechst AG, Frankfurt and Department of Epidemeology, Technical University of Munich.

Figure 1 - Page 14 from submission (Hoechst Epi Study)

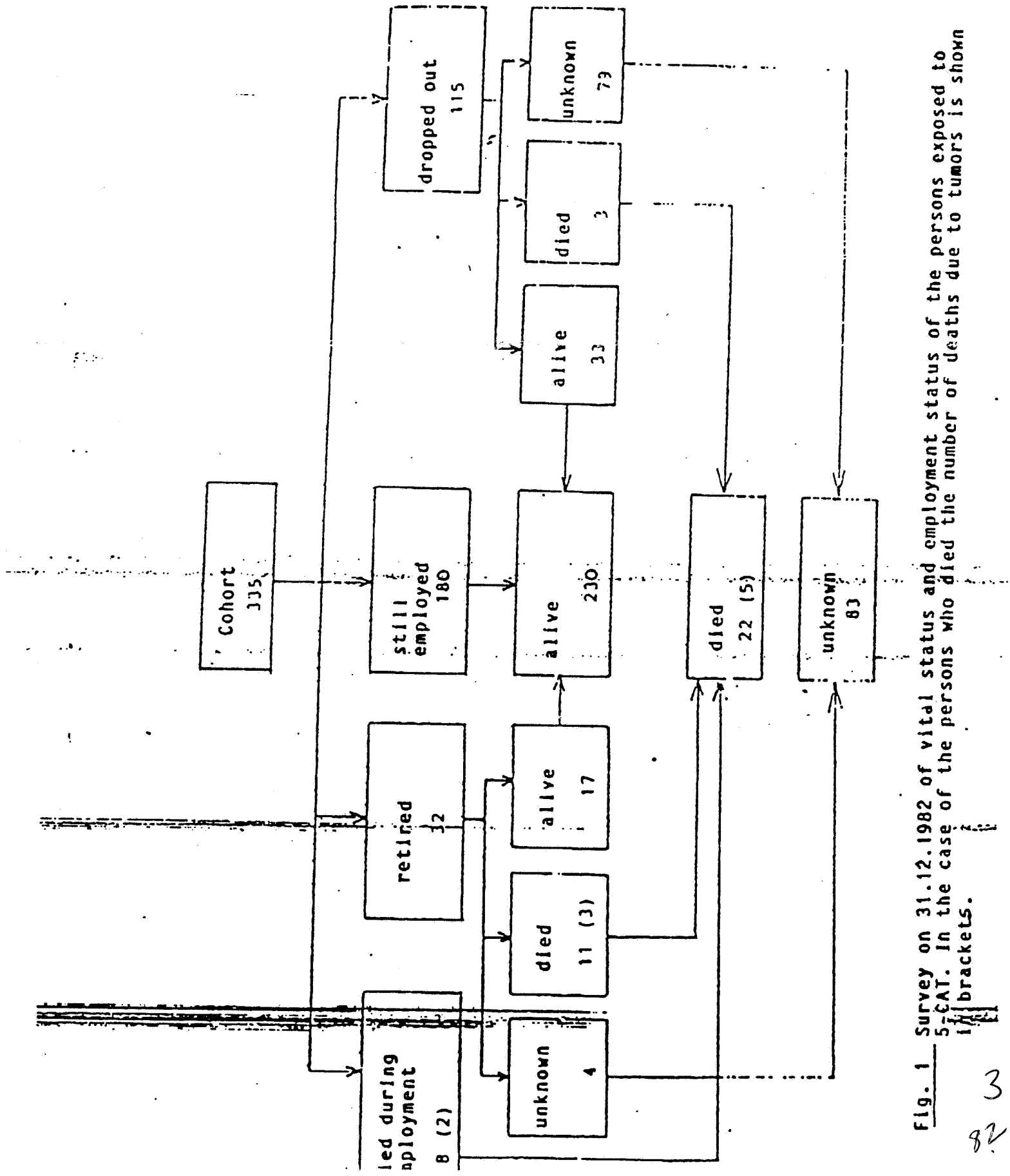


Fig. 1 Survey on 31.12.1982 of vital status and employment status of the persons exposed to 5-CAT. In the case of the persons who died the number of deaths due to tumors is shown in brackets.

Table-2 (page 16 from submission) 16

Table 2: Standard mortality rates (SMR) for the total collective (n = 335)

Cause of death	ICD - No. 9th Rev.	Mortalities observed	expected Hesse	expected FRG	S M R Hesse	S M R FRG
Total causes of death	000 - 999	22	25.06	27.13	0.88	0.81
Malignant neoplasms	140 - 199	5	4.89	5.13	1.02	0.94
- stomach	151	2	0.73	0.86	2.72	2.34
- urogenital	179 - 189	1	0.67	0.68	1.50	1.46
- brain	191	2	0.10	0.11	19.93**	18.80**

* P < 0.05
** P < 0.01

Table 3 (page 17 from submission)

Table 3: Standard mortality rates (SMR) for the partial collective: "start of exposure before 1970," (n = 116)

Cause of death	ICD - No. 9th Rev.	Mortalities observed	expected Hesse	expected FRG	S M R Hesse	S M R FRG
Total causes of death	000 - 199	19	17.03	18.31	1.12	1.04
Malignant neoplasms	140 - 199	5	3.45	3.75	1.45	1.33
- stomach	151	2	0.56	0.65	3.60	3.10
- urogenital	179 - 189	1	0.49	0.51	2.04	1.98
- brain	191	2	0.06	0.06	35.21**	31.67**

4

93

* P < 0.05

Table 2 Major neoplastic changes found in the pathological examination of mice after dermal applying ethyl-chlordimeform

Group and Treatment	Skin					Liver					Lung			
	No of exam.	Carc.	Tumor	Hyper-plasia	Neg.	No of exam.	Carc.	Tumor	Hyper-plasia	Neg.	No of exam.	Carc.	Tumor	Negativ
Positive control Coal tar pitch, CO	18	88.9	11.1	0.0	0.0	19	15.8	5.3	0.0	78.9	19	26.3	15.9	57.9
CDM 4000 mg/kg, CO	15	60.0	13.3	13.3	13.3	16	18.8	6.2	0.0	75.0	12	33.3	11.3	33.3
CDM 2000 mg/kg, CO	13	20.0	20.0	26.7	33.3	14	14.3	0.0	0.0	85.7	12	33.3	33.3	33.3
CDM 500 mg/kg, CO	23	4.4	4.4	52.2	39.1	25	8.0	0.0	4.0	88.0	14	14.3	28.4	57.1
CDM 100 mg/kg, CO	19	0.0	5.3	21.1	73.6	21	23.8	0.0	9.5	66.7	16	6.3	25.0	68.8
CDM 500 mg/kg	22	4.6	4.6	18.2	72.7	20	25.0	0.0	0.0	75.0	18	11.1	16.7	72.2
Promotor control Croton oil 30 times	17	0.0	0.0	17.6	82.4	24	0.0	0.0	8.3	91.7	18	11.1	33.3	55.6
Negative control Water applying 30 times	18	0.0	0.0	6.1	93.9	17	0.0	0.0	0.0	100.0	18	2.5	12.5	75.0

Abbreviations: CDM Chlordimeform
CO Croton oil applied 30 times
Carc. Carcinoma

According to Dr. Allan L. Black of the National Health and Medical Research Council of Australia (his letter of November 18, 1986 to Dr. Robert I. Krieger of the California Department of Food and Agriculture), this study was presented orally at the Medichim Conference, Bahia, Brazil in September, 1985. In it Black also states that Hoechst had recently advised the German authorities that 7 cases of bladder cancer have been found in the follow-up of the Stasik study. Dr. Black also indicated that Germany will change the classification of this chemical from A2 (animal carcinogen) to an A1 or human carcinogen. A Hoechst AG letter of September 3, 1986 to Dr. P. Dubach of Ciba-Geigy Basle, referred to 5 cases of bladder cancer (rather than 7) and noted that Hoechst was stopping its manufacture of 4-chloro-o-toluidine.

Summary of Dye Worker Study. Three hundred thirty five male workers who had worked in the Hoechst dye plant in Germany from 1929 to 1982 were evaluated. It was noted that a new plant was built in 1971 (in which worker exposures to chemicals were reduced). The workers in the study were said to have been exposed to 5-CAT (4-chloro-2-methyl aniline) for at least 12 months. There were no data presented which attempted to quantitate the type and amount of exposure to the workers. The fate of the workers as of 1982 was summarized in Figure 1 taken from the report. The overall causes of death compared to standard mortality ratios (Table 2, from the report) indicated that the mortality rates of these workers was better expected (referred to as the "healthy worker effect").

Of the 335 workers, 5 of them developed cancer of the stomach, prostate and brain. The overall tumor rates were approximately normal, however, the brain tumors (observed in 2 workers) was considered higher than expected.

Comments: 1) Characterization of exposure. The autnors of the present report also refer to a previous report by Ott and Langner (Ott, M.G. and Langner, R.R., A mortality survey of men engaged in the manufacture of organic dyes, J. Occup. Med. 25:763, 19??) in which the workers were exposed to o-toluidine and 4-chloro-o-toluidine as well as 5-CAT. Dr. Heiz Trebitz of American Heochst Corporation, New Jersey, indicated verbally to this reviewer (1/8/87) that the workers in the Hoechst plant in Germany were exposed to a variety of different chemicals. Apparently workers in dye factories are exposed to a number of chemicals which are considered oncogenic (personal conversation with Dr. Elizabeth Weisberger, NCI, 1/8/87) which makes it difficult to relate any bladder cancer findings to exposures to only 5-CAT.

It should be noted that exposures in the older plant, from 1929 to 1971, probably involved high exposures to a variety of chemicals. Table 3 (from the report) indicates that workers followed up to 1970 (n=116), had incidences of neoplasms that

were greater than expected. Therefore, before one can single out 5-CAT as the cause of any tumors in these workers, it will be necessary to obtain specific information on both the quantitative and qualitative aspects of worker chemical exposures.

2) Tumorigenicity. Two of the workers in the present study developed brain turmors. Brain tumors were not reported in previous epidemeological studies nor have brain tumors been prominent in any of the animal studies reviewed by the Agency. The primary tumors of concern in animal studies have been hemangioepitheliomas found only in the mouse.

Relative to bladder involvement in humans, hemorrhagic cystitis had be reported in 1933, 1978 and 1982 studies involving massive short-term exposures to chlordimeform. None of the animal studies indicated bladder neoplasia. Bladder cancer, however, has been associated with a number of aromatic amines (not 4-chloro-o-toluidine specifically) which may have been used in the Hoechst plant (Weisberger, 1975).

Conclusions. 1) Documentation for the bladder cancers in the Hoechst plant has not been provided. 2) There remains a question of the actual exposures in these workers relative to the chemicals involved and the amount of exposure. 3) Therefore the results of this investigation impacts on the Special Review process only to the extent that these questions are unanswered.

Additional Background Resources Used

1) Call to Dr. Heinz Trebitz, American Hoechst Corp., New Jersey. 1/8/87.
2) Call to Dr. Eizabeth Weisberger, NCI. 1/8/87/
3) Consult with Jerry Blondell, EAB, 4/17/87 relative to the study deficiencies.
4) Contacted a variety of references on human carcinogens and dye plant exposures.
5) Aromatic Amines, pp 339-343 in Chemical Carcinogenesis, John H. Weisburger, in Casarett and Doul's Toxicology, Macmillan, 1975.

B. Dermal Study Oncogenicity Study in Mice.

Study: Study of the Carcinogenicity of Chlordimeform--Report of Dermal Carcinogenicity Bioassay of Chlordimeform in Mice. J. Xue-zhi, X. Shou-zhen, Li feng, W. Yi-lan. School of Public Health, Shanghai Medical University. Occupational Health Bulletin. Selected Papers/Abstracts. Volume I, 1985. (Translation).

Study Design: Little detail was provided in this summary. Four hundred male Swiss mice of three months age were divided into 8 groups as shown in Table 2 taken from the report. The

mice were treated with coal tar pitch as a positive control; water as a negative control, and croton oil (0.5% in acetone) as a promotor control. Purified chlordimeform (98% pure) was desolved in the croton oil/acetone solution in levels to apply CDM as 100, 500, 2000, and 4000 mg/kg to the backs of the mice. In one dosage group, 500 mg/kg of chlordimeform was applied without the croton oil. No comment concerning a vehicle for this group was made. These materials were applied to the interscapular regions of the mice twice per week for varying periods which ranged from 17 to 30 application times. It is not clear if the application site was protected with a cover or not.

The animals were examined grossly each day and were necropsied at some time (not specified) when the tissues were taken for histological evaluation. Quantitative histological results were presented for the skin, liver and lung (Table 2), with a few general comments for some of the other organs. It should also be noted that Table 2 refers to "ethyl-chlordimeform" rather than methyl chlordimeform which is used in the U.S.

Discussion. We cannot ascertain whether the chlordimeform used in this study is the one of concern to us in this country. This may be a translation error. The results shown in Table 2 suggest a significant increase in the incidence of skin carcinoma and possibly in lung tumors, however, the role of croton oil and acetone in accellerating neoplastic effects is a complicating factor. The numbers of animals in each group which made it to necropy is considerably less than the 50 animals originally assigned to each group and raises questions concerning the survivability, care in handling, etc.

Conclusions. 1) The test agent is in question. 2) The role of vehicles probably influenced the results of the study. 3) The laboratory practices may have been faulty. 4) Therefore the findings should not incorporated into the Special Review at this time. Because of its known tumorigenicity, the Agency has already imposed measures to keep workers from getting CDM on their skin.

C. Life-Time Feeding Study in Mice.

Study. Carcinogenic Effects of Chlordimeform in Mice from Life-Time Oral Dosing Experiment (Feeding rather than gavage) L. Feng, Z. Shan Ching, H. Tsi Kwang. Department of Occupational Health, Shanghai First Medical College. and C. See Ah, W. Y. Fong (Department of Preventive Medicen, Shanghai Medical College, Shanghai. Occupational Health Bulletin. Selected Papers/Abstracts. Volume I, 1985. (Two translations are available, one provided in the Ciba-Geigy letter of November 14, 1986 and a somewhat expanded translation provided with the Ciba-Geigy letter of October 7, 1986, EPA Accesssion no. 265191).

81

Study Design. Only a summary statement of the study was provided. Five groups of male weanling Swiss mice, 50 per group were exposed to 20, 100, and 300 ppm of chlordimeform (99% pure) mixed in their diet. Control animals were fed the diet without the chlordimeform while a 5th group of animals were fed a diet containing 300 ppm of p-chloro-o-toluidine.

Results. Table 1 (taken from November 14 submission) shows a strong increase in the benign tumors (neoplasms) and malignant tumors with increasing dose of CDM. The 300 ppm CDM group was similar to the 5-CAT treatment group. There was a tendency for the latency period to decrease with increasing exposure to CDM, and a marked decrease in the latency time for the 5-CAT treatment group. The distribution of the oncogenic finding is presented in Table 2 taken from the report. Angiomas predominated as the key neoplastic response while angiosarcoma was only slightly increased in the CDM treatment groups. This in contrast to the marked development of hemangioepitheliomas seen in the mouse studies in this country.

Discussion. This is a summary report (translation) of a study which would require much more information than was presented. Therefore it is not possible to validate this study. The results presented indicate that the study may have significant differences for the previous mouse studies reviewed by the Agency. Angiomas and lung tumors were not prominent in other mouse studies reviewed by the Agency. There may be differences in terminology for the pathological findings.

Recommendation. 1) There are some differences in the results of this Chinese study compared to those already reviewed by the Agency. 2) The significance of these differences cannot be established; however, based on the mouse studies available, CDM is a potent mouse carcinogen. 3) These findings do not significantly effect the Special Review for CDM.

D. Occupational Exposures in Chlordimeform Plant Workers.

Study: Investigation of Occupational Hazards of Chlordimeform Packing. Ding Yue, et.al. (sic). Dept. of Occupational Health. Hua-Shan Hospital, Shanghai Medical University. Occupational Health Bulletin. Selected Papers/Abstracts. Volume I, 1985. (Translation).

Study Design. Twenty eight workers from a Chines packing plant were evaluated over a five month period for possible toxic signs and symptoms while working with chlordimeform hydrochloride (25%) formulation. The workers wore rubber gloves as the only protective measure. Airborne levels and urinary levels were monitored initially and five months later. The report listed the incidence of headache, fatique, nightmares, abdominal pain, nausea, numbess of the extremities, hypertension, hypotensions, leukopenia, mild anemia, tachycardia, ventricular ectopic beats, etc.

(Mouse feeding onco. Study)

Table 1. General Aspects of the Assay (Page 108)

Group	Dosage (in diet)	No. of Animals Necropsied	No. of Animals Bearing Neoplasm	Rate %	No. of Animals Bearing Malignancy	Rate	Day first detected bearing Neoplasm
1	CDM 0	50	0	0	0	0	-
2	20 ppm	50	8	16	0	0	494
3	100 ppm	50	22	44	5	10	469
4	300 ppm	50	36	72	15	30	448
5	p-C-o-T 300 ppm	50	31	62	13	26	283

Results of the histopathological examination were showed in table 2.

Table 2. Histopathological Findings (Page 109)

Neoplasm	Group				
	I	II	III	IV	V
Angiosarcoma	0	0	0	2	10
Angioma	0	6	15	24	19
Pulmonary carcinoma	0	0	3	6	4
Pulmonary adenoma	0	0	3	4	0
Liver cancer	0	0	1	2	1
Splenic lymphosarcoma	0	0	0	1	0
Renal adenocarcinoma	0	0	1	1	4
Renal adenoma	0	0	1	0	1
Stomach adenoma	0	1	0	0	0
Intestinal carcinoma	0	1	0	4	0
Other sites					
Cancer	0	0	1	1	0
Tumor	0	0	0	1	0
Nodular growth in liver	0	1	7	9	1
Fatty degeneration in liver	0	4	10	17	3

Results Airborne levels ranged from 0.0 to 0.008 mg/cu.m. initially and 0 to 0.33 mg/cu.m. five months later. Urine measurements for 5-CAT initially were 0.048 mg/l (0.0- 0.018) and 0.151 mg/l (0.025-0.478) five months later.

The incidence of the signs and symptoms were reported in the text of the abstract. ~~(page 110, attached).~~ The findings occurred in low frequency (1 or 2) for more serious findings such as abdominal pain, hypertension, leukopenia compared to up to 3 individual from complaints of headache and fatique. None of these seem to be toxic signs relatable to chlordimeform exposures. The authors note than there were no changes in the types of complaints experienced by these workers.

Discussion: The authors concluded that there were no "chronic" effects from the exposure to chlordimeform, however the urinary excretion increased in value and may indicate long-term hazards. The exposure levels in these studies are probably not much different then the worker exposures monitored by Ciba-Geigy USA.

The Chinese workers did not experience any of the signs and and symptons, expecially the hemorrhagic cystitis, experienced by the U.S. chlordimeform packing workers reported by Follon et al. (report in JAMA, 1978). Other toxic problems in humans described by Ciba-Geigy were epistaxia, hyperpyrexia, skin irritation, asthma, alopecia, and dizziness. None of these symptoms were seen in the Chinese study.

Conclusions. 1) It is difficult to evaluate that exposures quantitatively based on the information provided. 2) The complaints experienced by these workers were not similar to complaints reported by workers in this country who had high exposure rates. 3) The results presented in this brief summary do not affect the current Special Review process.

Additional Background Materials Used

1) Chlordimeform in "Pesticides Studied in Man", W.J. Hayes, Williams and Wilkings, 1982.

2) Ciba-Geigy Corporation submission of background information, 1984.

E. Chinese Farm Worker Excretion Study.

Study: Investigation on the Kinetics of Excretion of Chlordimeform in Sprayers (A Preliminary Report). Wang Ming, Xue Shou-zhen, et al. Department of Occupational Health School of Public Health, Sanghai Medical University. Occupational Health Bulletin. Selected Papers/Abstracts. Volume I, 1985. (Translation).

Study Design. The urinary metabolites of chlordimeform of sixteen farmers who had been manually spraying cotton with sackpack sprayers for three days were measured during the 3 days application period and 5 consecutive days following the spraying activity. Spot urine samples were obtained from the farmers before the work shift, after the work shift and in the evening before going to bed. The urine concentration was adjusted for volume by the creatinine level found in the urine. The urinary metabolites were determined as chlordimeform and metabolites convertable to p-chloro-o-toluidine.

Chlordimeform was measured in the breathing zone of the workers, however, the data for such measurements were not presented. The authors only indicated that the mist in the breathing zone was "generally low". The form of chlordimeform (base or salt?) was not specified. Whole body surface contamination was estimated by the method of "regional proportional swab wash strategy" (not desribed). These results were also not reported.

Results. The results are summarized in Figure 1 (page 112 from the report which also included the kinetic constants derived in the study. The authors concluded that the uptake (mostly through the skin) was rapid with a half-life of 1.53 hours and was characterized as the three peaks in Figure 1. The excretion pattern at the end the three work days was described as including a fast phase with a half-life of 11.56 hours and a slow phase with a half-life of 70 hours. The investigators assumed a two compartment model and provided numbers shown on page 112 which correspond to the transfer coefficients for the compartments.

Discussion. It is not clear whether these workers were exposed to chlordimeform base or chlordimeform hydrochloride salt. There were no data on which to base the amount of exposure of the farm workers, however, the amount of chlordimeform/metabolites appearing in the urine suggested high exposure rates. Further, it is not possible to determine acurately the total amounts of CDM that is excreted by each worker because the results are expressed as concentrations rather than total amounts.

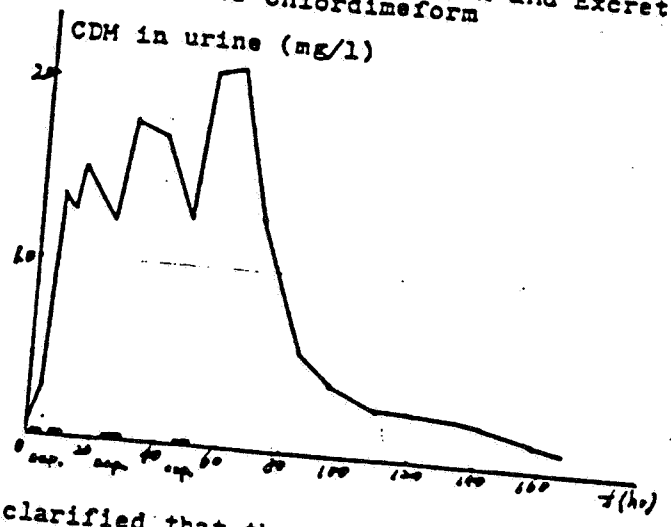
The rapid excretion phase (T/2 = 11.56 hours) was comparable to that reported by Nixon and Neal (T/2 = 8.8 hours) in the Ciba-Geigy worker study. However, the Nixon and Neal data do not suggest the prolonged excretion rates relating to the slow phase of excretion which may be important relative to allowing enough time for removal of CDM before allowing additional exposure.

These data also show how readily CDM can accumulate in workers who were exposed under repeat (daily) exposures. The reporting of averages without individual data does not allow the presentation on individual variation seen in these workers.

It is not possible to determine from the report, what

(Farmer Excretion Study)

Fig. 1. The Curve of Absorption and Excretion of Chlordimeform



It is clarified that the absorption and excretion of Chlordimeform in human body follows first order rate and fits the two compartments model. Principal parameters derived from kinetic calculation are as follows:

Absorption phase: absorption rate constant $k_a = 0.4531\ h^{-1}$

Excretion phase: fast phase $T = 1.53h$, $\alpha = 0.0610\ h^{-1}$

slow phase $T = 11.56h$, $\beta = 0.0099\ h^{-1}$, $T = 70.00h$

Constants for transfer rate: $k_{12} = 0.0216\ h^{-1}$, $k_{21} = 0.0269\ h^{-1}$, $k_e = 0.0226\ h^{-1}$

Rate of urinary excretion

$$x_d = 2.123\ e\ (\text{Exp}\ -0.0610t) + 0.918\ e\ (\text{Exp}-0.0099t) - 3.041\ e\ (\text{Exp}-0.4531t)$$

x_d: the urinary Chlordimeform excretion mg/l

t : time in hour after exposure

Results suggest that: the absorption of chlordimeform through intact skin is relatively quick, and the excretion rate is rather slow. Though it follows two compartments model, the absorbed Chlordimeform is mainly stay at the central compartment for $k_{21} > k_{12}$. Accumulation in short period of time is possibly existed.

13

92

data was used to determine that chlordimeform was handled in two compartments within the body, the relationships of the two compartments, etc.
of the two compartments.

Recommendations. 1) This summary presents interesting data which should be important to our understanding of the uptake and excretion of CDM. It suggests that CDM can accumulate more readily than it is excreted. It also indicates that the rate of excretion (half-life in the body) varies with the amount in body suggesting longer periods of time may be necessary for the body to rid itself of CDM than previously thought. 2) It is therefore desirable to obtain more information that is probably available from this study. 3) None of the information provided should significantly alter the Special Review process, but should be used to raise the questions in the review concerning the kinetics noted here.

Additional Background Material Used.

1) Nixon, W.B. and Neal, B.E. "Chlordimeform residuses in human uring following dermal application". Ciba-Geigy Corporation Report #ABR-83017, 7/11/83.

2) Memoranum: Chlordimeform. EPA Registraton No. 100-560. Urinary excretion after dermal absorption in humans. EPA Access. No. 254914.

3) Consultations on kinetics (Joel Garbus, Linda Kutney, and others.

4) "Pharmacokinetics in Toxicology" pp. 659-689, by A.G. Renwick, in Principles and Methods of Toxicology, A.W. Hayes, Raven Press, 1982.

5) Mathematical Techniques for Physiology and Medicine. W. Simon, Academic Press, 1972.

6) Toxicants and Drugs: Kinetics and Dynamics, E. O'Flaherty, John Wiley and Sons, 1981.